4th International Conference on Computational and Mathematical Biomedical Engineering - CMBE2015
29 June-1 July 2015, France
P. Nithiarasu and E. Budyn (Eds.)

MODELLING AND SIMULATION OF CELL MIGRATION IN HETEROGENEOUS MEDIA

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SUMMARY

We present a framework for the modelling of cell motility in heterogeneous environments. The cell membrane is represented by an evolving surface, with the movement of the cell determined by the interaction of forces that act normal to the surface. The biochemistry is modelled through partial differential equations posed on the cell membrane. For the mechanics, we propose a force balance on the surface, including external forces to model inhomogeneities in the medium such as other cells, adhesion to a substrate and obstacles. We employ a computational method based on evolving surface finite elements for the simulation of the model and report on a number of simulation results illustrating the applications of the approach.

Key words: *cell motility, surface finite elements, elastic membranes, adhesion, obstacles*

1 INTRODUCTION

Understanding cell motility, the directed motion of cells, is of importance due to the central role it plays in several biological phenomena such as embryonic development, cancer, tissue development and immune responses. Coupling modelling with experiments appears indispensable in furthering our understanding of the complicated processes involved [1]. Simulation of cell motility necessitates the consideration of evolving geometries and is a formidable computational challenge.

This work builds on [2] in which we presented a mathematical framework for the modelling of cell motility and a numerical method for the simulation of such models. The approach consists of partial differential equations posed on the cell boundary coupled to an evolution law for the cell membrane. In this work we focus on the inclusion of external forces to model heterogeneity in the medium in which the cell migrates. The numerical method for approximating the model, based on evolving triangulated surfaces, consists of an evolving surface finite element method [3, 4] for the approximation of the surface partial differential equations that model the biochemistry and a parameterised finite element method [5] for the approximation of the surface evolution law that models the mechanics.

2 MODELS AND METHODS

The cell membrane is represented by a smooth closed smoothly evolving hypersurface $\Gamma(t)$, with the movement of the cell determined by the interaction of various forces that act normal to the cell membrane. We consider external forces such as a a pressure that constrains the enclosed volume, as well as internal forces that arise from the reaction of the cell surface to stretching and bending. We use the following force balance on the membrane:

$$0 = \left(\mathcal{F}_{prot} + \mathcal{F}_{vol} + \mathcal{F}_{visc} + \mathcal{F}_{ext} + \mathcal{F}_{surf} + \mathcal{F}_{bend}\right)\boldsymbol{\nu}, \tag{1}$$

where $\boldsymbol{\nu}$ denotes the outward pointing unit normal to the surface Γ. The assumed force balance leads to the following equation for the evolution of the cell boundary:

$$\boldsymbol{V} = \left(\boldsymbol{k}_p \cdot \boldsymbol{a} - k_s H + k_b\left(\Delta_\Gamma H + H\left|\nabla_\Gamma \boldsymbol{\nu}\right|^2 - \frac{1}{2}H^3\right) + \lambda + \mathcal{F}_{ext}\right)\boldsymbol{\nu}, \tag{2}$$

where $\boldsymbol{V}$ is the material velocity of points on the cell surface (which is has zero tangential component due to the assumption of only normal forces), $\boldsymbol{a} = (a_1, \ldots, a_{n_a})^T$ denotes a vector of species resident on the cell surface (e.g., actin, myosin, etc.,), $\boldsymbol{k}_p \in \mathbb{R}^{n_a}$ governs whether each species promotes protrusion or retraction of the cell membrane, H is the mean curvature of Γ, k_s the surface tension, k_b the bending rigidity, Δ_Γ and ∇_Γ are the Laplace-Beltrami and surface gradient operators respectively, $\boldsymbol{\nu}$ denotes the outward pointing unit normal to Γ, λ denotes a (spatially uniform) Lagrange multiplier that enforces volume conservation and $\mathcal{F}_{ext}$ are external forces (acting normal to the surface).

For the surface resident species $\boldsymbol{a}$ appearing in (2), we consider an RDS posed on an evolving surface $\{\Gamma(t)\}_{t>0}$:

$$\partial^\bullet \boldsymbol{a} + \boldsymbol{a}\nabla_{\Gamma(t)} \cdot \boldsymbol{V} - \boldsymbol{D}\Delta_{\Gamma(t)}\boldsymbol{a} = \boldsymbol{f}(\boldsymbol{a}) \quad \text{on } \Gamma(t), t > 0, \tag{3}$$

where

$$\partial^\bullet \boldsymbol{a} := \partial_t \boldsymbol{a} + \boldsymbol{V} \cdot \nabla \boldsymbol{a}, \tag{4}$$

is the material derivative with respect to the velocity $\boldsymbol{V}$, $\boldsymbol{D}$ is a diagonal matrix of positive diffusion coefficients and $\boldsymbol{f}(\boldsymbol{a})$ is the reaction.

We now summarise the additions to the modelling we consider in this work, i.e., the incorporation of adhesion and the inclusion of obstacles.

2.1 A model for adhesion

To include adhesion in the model we propose a Lennard-Jones adhesion potential of the form

$$\mathcal{E}_{adh} = \int_\Gamma W(d) := \int_\Gamma \gamma \left(\left(\frac{\beta}{d(\boldsymbol{x})} \right)^\alpha - \left(\frac{\beta}{d(\boldsymbol{x})} \right)^{\alpha/2} \right) \mathrm{d}\boldsymbol{x}, \tag{5}$$

where $d(\cdot)$ is the distance function to the object the cell adheres to and $\gamma, \alpha \in \mathbb{R}^+$ are parameters governing the strength and range of the potential. The potential is repulsive at very short distances, attractive at medium distances and rapidly decays to zero at long distances and hence is a reasonable model for adhesion between two surfaces that can not intersect. The corresponding force contribution to the evolution law may be derived consistently as in [6] and yields

$$\mathcal{F}_{adh} = -W'(d)\nabla d \cdot \boldsymbol{\nu} - W(d)H.$$

2.2 Obstacles as a hard constraint

In [2] we proposed a model for migration in the presence of obstacles with the interaction between the cells and the obstacles modelled with a repulsive potential. In this work we propose an alternative model for the inclusion of obstacles in which the obstacles are treated as a "hard" constraint. We assume a set of smooth disjoint obstacles such that the boundary of the obstacles consists of smooth closed surfaces which may be described by a smooth level set function, ϕ_{obs} say, such that, ϕ_{obs} is positive outside the obstacles, ϕ_{obs} is negative inside the obstacles and $|\nabla\phi_{obs} \neq 0|$.

Our model for cell migration in the presence of obstacles consists of the coupled geometric evolution law surface RDS system (2) and (3) together with the constraint $\phi(\boldsymbol{x}) \geq 0$ for all $\boldsymbol{x} \in \Gamma(t)$.

2.3 Discretisation

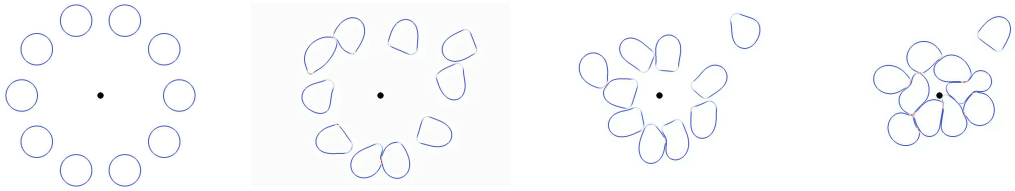
The numerical methods we employ are based on moving triangulated surfaces. Hence, equations posed on a surface that is d-dimensional are approximated with a d-dimensional algorithm. The method for the approximation of (2) is based on the parametric finite element method derived in [5]. Under the method the movement of the nodes of the triangulation satisfies the evolution law in the normal direction and includes a tangential velocity (that leaves the evolution law unchanged) which gives highly desirable mesh-properties in practice. The surface RDS is discretised with an ALE-evolving surface finite element method analysed in [4] which accounts for the fact that the vertices of the triangulated surface are moved with a velocity that is not Lagrangian. We use quadratic

elements for consistent approximation of the geometric evolution equation. For efficiency, we employ an adaptive meshing strategy with an heuristic adaptivity criterion based on the local mean curvature and adaptive timestepping strategy with an heuristic adaptive strategy based on the normal velocity of the surface. The linear systems are solved either using a direct solver or in the case of obstacles the variational inequality is solved using a projected SOR algorithm.

3 RESULTS

We conclude with some simulation results illustrating the efficacy of the methodology, in the interests of space we only briefly summarise the mathematical models and omit the details on the parameter values used.

3.1 Simulation of adherent cell chemotaxis: cell-cell adhesion



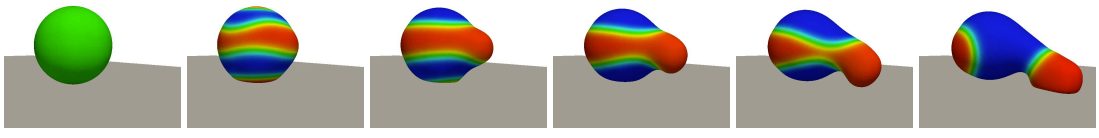
(a) $t = 0$. (b) $t = 2$. (c) $t = 5$. (d) Ligand source reached.

Figure 1: Multi-cell chemotaxis with cell-cell adhesion.

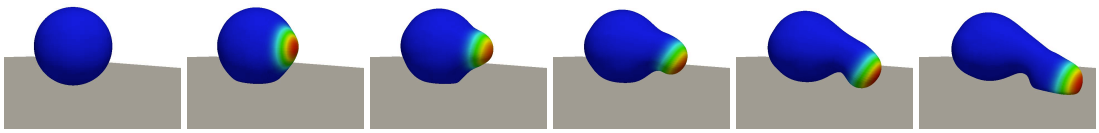
Figure 1 shows the results of a simulation of the chemotaxis of multiple cells. The surface RDS is taken to be the Meinhardt model for chemotaxis used in [2, 7], we incorporate cell-cell adhesion by including a Lennard-Jones potential between each of the cells. The cells are taken to be initially circular and distributed in a ring around a source of ligand. The ligand density is assumed to be time independent and to decay exponentially away from the source. We observe chemotaxis of the cells towards the ligands via biased generation of pseudopods and adhesion between cells with no interpenetration of cells.

3.2 Simulation of adherent cell migration: cell-substrate adhesion

To model adhesion to a substrate we include another surface resident species corresponding to surface binders which form adhesions with the substrate. The Lennard-Jones potential is now weighted by the surface binder density i.e., γ in (5) is a function of the surface binder density. The evolution of the surface binders satisfies a surface Cahn-Hilliard type equation based on the model of [8]. We keep the Meinhardt surface RDS used in 3.1 to generate protrusion. Figure 2 shows the results of a simulation of adhesion, with the binders moving into the protrusion which then adheres to the substrate.



(a) Surface binder density at $t = 0, 1, 2, 3, 4$ and 5 reading from left to right.

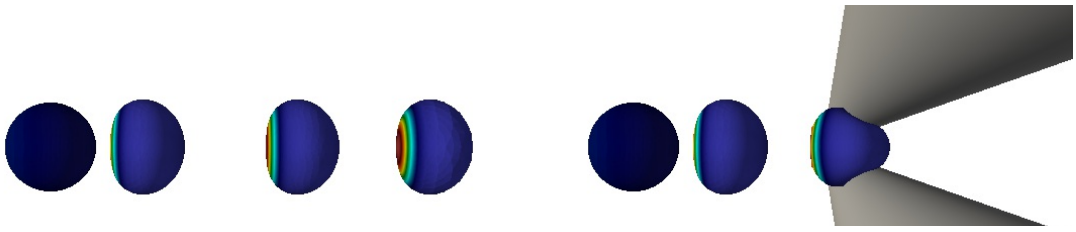


(b) Surface RDS activator density at $t = 0, 1, 2, 3, 4$ and 5 reading from left to right.

Figure 2: Migration of an adherent cell on a substrate.

3.3 Simulation of cell migration in the presence of obstacles

We conclude with a simulation of cell migration in the presence of obstacles. The model is based on the model for the motion of fish epithelial keratocytes presented in [2]. Under the model (in the absence of obstacles) the cells exhibit steady directed motion in a fixed direction with a constant speed (c.f., [2] and Figure 3(a)). When we include two cylindrical obstacles that the cell can not penetrate (Figure 3(b)) we observe that the cell is trapped by the obstacles and by $t = 3$ has attained a steady state in which the cell is stationary.



(a) Migration without obstacles $t = 0, 1.5, 3$ and 4 from left to right.

(b) Migration with obstacles $t = 0, 1.5$ and 3 from left to right.

Figure 3: Cell migration with and without obstacles.

4 CONCLUSION

We have presented a modelling and computational framework for simulating cell migration in heterogeneous media. The computational method employed is robust and efficient and we illustrated its efficacy by simulating multicell chemotaxis, adherent cell migration, and migration in the presence of obstacles. The next steps will be to validate the modelling and simulations against experimental observations such as in vitro studies of cell migration in biomaterial scaffolds.

5 ACKNOWLEDGEMENTS

VS and CV acknowledge financial support from the EPSRC grant EP/J016780/1 and the Leverhulme Trust Research Project Grant (RPG-2014-149).

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